REMARKS

Objections Raised by the Examiner

Sequence Listing

The Examiner objects that the application fails to comply with the sequence listing requirements of 37 C.F.R. §§ 1.821(a)(1) and (a)(2). Applicants respectfully submit that the application is, and since at least April 2001 has been, fully in compliance with the aforementioned requirements.

On April 2, 2001, the Examiner mailed a communication and Notice to Comply with the sequence rules. On April 16, 2001, applicants mailed a response containing a substitute paper copy of the sequence listing and a substitute computer readable form (CRF) of the sequence listing fully compliant with the Examiner's request and relevant rules.

In the Notice to Comply that accompanies the current office action, the Examiner refers applicants to the raw sequencing listing mailed April 2, 2001 by the PTO. Applicant's April 16, 2001 response had by that time addressed the problems identified therein: in the <213> fields, applicants replaced all occurrences of the "Artificial/Unknown" notation with either "Artificial Sequence," or the genus/species scientific name, as appropriate. Applicants respectfully invite the Examiner to review the applicant's April 16, 2001 submission.

The Examiner states that the Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) is not in receipt of the substitute computer readable form (CRF) submitted with the response mailed April 16, 2001. Enclosed herewith in Appendix A is a copy of the postcard that accompanied the substitute CRF and other papers, as stamped by

the O.I.P.E. on April 23, 2001 and returned to our offices. None of the items listed on the postcard were crossed off and initialed. Therefore, the postcard is prima facie evidence that the substitute CRF was received by the P.T.O. on that date. See M.P.E.P. § 503.

In the interests of advancing prosecution, applicants resubmit herewith a copy of the April 16th, 2001 substitute paper copy of the sequence listing and substitute CRF of the sequence listing.

Declaration

The Examiner objects that the Declaration filed under 37 C.F.R. § 1.63 is defective because it is required to cite priority to the provisional application by explicit, literal, and *ipsis verbis* reference to subsection "(e)" of 35 U.S.C. § 119. To the best of applicants' knowledge, no such requirement exists, either in law or in lore. It is commonly understood that reference to a statutory code section includes a reference to all pertinent subsections. Thus, reference to "35 U.S.C. § 119" necessarily includes reference to "35 U.S.C. § 119(e)." Applicants believe that they have fully complied with the requirements of § 119(e) by referring specifically to the priority provisional application in the pending application. The Examiner's objection is therefore in error and should be withdrawn.

Information Disclosure Statement

The Examiner objects that "the information disclosure statement filed 5/19/00 fails to comply with 37 C.F.R. 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that

portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered."[1] Applicants respectfully submit that they have for 18 months been fully in compliance with the requirements of 37 C.F.R. §§ 1.56, 1.97 and 1.98. The Examiner's objection is therefore in error and should be withdrawn.

On May 15, 2000, applicants transmitted to the P.T.O. an information disclosure statement, Form PTO-1449 in duplicate, a transmittal letter in duplicate, one copy each of 148 documents listed both in the IDS and on Form PTO-1449, a check for $240.00, and a self-addressed receipt postcard specifying the identity of each of the aforementioned items. The postcard was stamped by the O.I.P.E. on May 19, 2000 and returned to our offices. A copy of the return postcard as so stamped is enclosed in Appendix A. None of the items listed on the postcard were crossed off and initialed. Therefore, the postcard is prima facie evidence that all 148 references sent to the P.T.O. were received by the P.T.O., and therefore should have been considered by the Examiner. See M.P.E.P. § 503.

In order to advance prosecution, applicants provide a second set of copies of the 148 documents submitted with the IDS of May 15, 2000, as well as copies of the original transmittal letter, IDS, and Form PTO-1449.[2]

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[1] Office action, p. 9, paragraph 13.

[2] Applicants wish to bring to the attention of the Examiner and PTO that, through no fault of applicants, the apparent loss of the first set of documents by the PTO has forced applicants to expend an additional $679.05 for copying fees, as well as unreported additional fees for shipping (see photocopy invoice in Appendix B).

Status of the claims

Claims 12 - 43 are pending and stand rejected.[3]

Applicants cancel claims 12 - 43 and add new claims 44 - 51 by amendment herein more particularly to point out and distinctly claim their invention. Applicants reserve the right to prosecute the subject matter of the canceled claims in one or more divisional or continuation applications. For the reasons set forth below, applicants submit that the amendments add no new matter.

Support for new claims 44 - 51 can be found throughout the specification, including drawings and claims as originally filed, and particularly as follows.

Support for new claims 44 and 49, and the claims depending therefrom, can particularly be found in the Summary of the Invention on page 6, line 28 - page 7, line 5 and in the Introduction to the Present Invention on page 24, line 10 - page 3, line 6.

Support for an antibody, as recited in claims 44 and 49, and the claims depending therefrom, is found on page 20, lines 1 - 15; page 22, line 19 to page 24, line 8; and the claims as originally filed.

Support for a moiety capable of binding to an FcRb receptor as recited in claims 44 and 49, and the claims depending therefrom, is found on page 6, lines 19 - 22; page 24, lines 29 -34; page 25, lines 1 - 5; page 25, line 13 - 36; page 26, lines 1 - 2; page 26, lines 26 - 36; page 27, lines 1 - 6 and lines 28 - 34; page 28, lines 14 - 27; page 38, lines

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[3] Applicants note that the "Office Action Summary" lists claims 12 - 43 as pending, with claims 27 - 43 withdrawn from consideration and claims 12 - 26 rejected. This appears to be error, inasmuch as applicants have not received a restriction requirement and the Examiner states on p. 2, paragraph 3 of the instant office action that claims 12 - 43 are pending and under examination.

33 - 34; page 39, lines 1 - 2; page 42, lines 25 - 32; page 43, lines 1 - 21; page 49, lines 1 - 18; and FIG. 1A and FIG. 1B.

Support for linking to the antibody at least a second moiety, as recited in claim 44, and the claims depending therefrom, is described throughout the specification as multimerized moieties, page 26, lines 9 - 11; tandem moieties, page 26, line 14; physically linking at least one moiety to a second moiety, page 24, lines 29 - 34; page 6, lines 28 - 32; page 7, lines 1 - 2; page 49, lines 11 - 18; page 50, lines 6 - 15; claims 1 and 2, as originally filed; the abstract; and the physical structure of linearly linked Fc regions is shown schematically in FIG. 1B.

Support for pH dependence of binding of FcRb receptor, and greater avidity of binding of FcRb receptor at pH 7.4, as recited by claims 44 and 49, and the claims depending therefrom, is found on page 3, lines 1 - 5; page 28, lines 6 - 13; page 53, lines 31 - 34; page 54, lines 16 - 21; and page 26, lines 4 - 24.

Support for FcRb receptor, as recited by claims 44 and 49, and the claims depending therefrom, is found particularly on page 24, lines 10 -15 and in Example 5 on page 53, line 9 - page 57, line 7.

Support for an immunoglobulin Fc region being capable of binding to an FcRb receptor, as recited by claim 45 and claim 48 depending therefrom, is found particularly on page 25, line 1 - page 26, line 2 and in FIG. 1A and FIG. 1B.

Support for an immunoglobulin hinge-CH2-CH3 region being capable of binding to an FcRb receptor, as recited by claim 46 and claim 48 depending therefrom, is found particularly on page 2, line 21 to page 4, line 36, and page 38, line 9 to page 43, line 21.

Support for an immunoglobulin CH2-CH3 region being capable of binding to an FcRb receptor, as recited by claim 47

and claim 48 depending therefrom, is found particularly on page 2, line 21 to page 4, line 36, and page 38, line 9 to page 43, line 21.

Support for an immunoglobulin CH3 region as recited by claim 49, and the claims depending therefrom, is found particularly on page 22, line 19 to page 24, line 8.

Support for an immunoglobulin CH2-CH3 region as recited by claim 50, and the claims depending therefrom, is found particularly on page 22, line 19 to page 24, line 8.

Support for an immunoglobulin hinge-CH2-CH3 region as recited by claim 51, is found particularly on page 22, line 19 to page 24, line 8.

Previously Pending and New Claims

Formerly pending, now cancelled, independent claims 12, 27, 42 and 43 are reproduced for reference below.

12. A method of extending the serum half life of a protein having a first region capable of binding to an FcRb receptor, the method comprising:
joining to said protein at least a second region capable of binding to an FcRb receptor.

27. A modified protein with an extended serum half life, said modified protein comprising:
a first region capable of binding to an FcRb receptor; and
at least a second region capable of binding to an FcRb receptor.

42. A method of increasing the avidity or affinity of a protein to a receptor, said protein having a first region capable of binding to said receptor, said method comprising
joining to said protein at least a second region capable of binding to said receptor.

43. A modified protein with enhanced avidity or affinity to a receptor, said modified protein comprising:
a first region capable of binding to said receptor; and
a linearly joined at least second region capable of binding to said receptor.

New independent claims 44 and 49, added by amendment herein, are reproduced for reference below.

44. A method of extending the serum half-life of an antibody having a first moiety capable of binding to FcRb receptor, the method comprising:
adding to said antibody at least a second moiety capable of binding to FcRb receptor in a pH-dependent manner,
wherein said antibody binds FcRb receptor with greater avidity at pH 7.4 after said linking.

49. An antibody with an extended serum half-life, said antibody comprising:
a first moiety capable of binding FcRb receptor; and
at least a second moiety capable of binding FcRb receptor,
wherein said at least second moiety confers upon said antibody avidity of binding FcRb receptor at pH 7.4 greater than that of said antibody lacking said at least second moiety;
wherein said at least second moiety binds FcRb receptor in a pH dependent manner, and
wherein said at least second moiety comprises an immunoglobulin CH3 region that contributes to FcRb receptor binding.

The Examiner's Rejections Under 35 U.S.C. § 112, ¶ 1 Have Been Obviated by Amendment or Are in Error and Should be Withdrawn

The Examiner has rejected claims 12 - 43 under 35 U.S.C. § 112, ¶ 1, for lack of adequate written description.

Applicants respectfully submit that the Examiner has misapplied the legal standard for written description to the rejected claims. For this reason alone, the Examiner's rejections under § 112, ¶ 1 are fatally defective and must be withdrawn. Furthermore, applicants submit that under the correct legal standard, the rejected claims, and the claims newly added by amendment herein, are adequately supported by the specification and reasonably convey to the skilled artisan that the applicants were in possession of the claimed invention at the time the application was filed. Thus, the Examiner's rejections would further be in error if asserted against the claims newly added by amendment herein.[4]

In support of the § 112, ¶ 1 rejections, the Examiner misquotes, without attribution, a section of the Federal Circuit opinion in The Regents of the University of California v. Eli Lilly and Co.,[5] thus applying a legal standard that speaks only to gene sequences to claims of an entirely different sort. Furthermore, the Examiner has failed to credit applicants' disclosure of physical and chemical properties, including complete and partial structures, and of correlations between function and structure, that provide the evidentiary basis for distinguishing applicants' specification over that at issue in Regents.

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[4] In commenting on the content of the rejected claims, the Examiner stated that "the instant claims encompass a protein and methods thereof, wherein the said protein comprises a first region and/or second regions can be any moiety that is capable of binding to an FcRb receptor and which is not an IgG Fc region or an IgG antibody." Office Action at p. 3, continuation of paragraph 6 (emphasis added). The latter part of the statement is incorrect. The claimed regions capable of binding FcRb receptor do not exclude IgG Fc or IgG antibody.

[5] The Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicants excerpt below that section of the Office Action[6] that quotes the Regents opinion[7], and point out where the Examiner has changed the text of the Federal Circuit's opinion. Text deleted by the Examiner is shown in bold within brackets; text added by the Examiner is shown underlined in bold.

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. **[In claims to genetic material]**, however, a generic statement such as **"a first region" and "at least a second region" "capable of binding to an FcRb receptor" ["vertebrate insulin cDNA" or "mammalian insulin cDNA," without more]**, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by **the property of being capable of binding to an FcRb receptor [function]**. It does not specifically define any of the **"regions" [genes]** that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by the **property of being "capable of binding to an FcRb" [function, as we have previously indicated]**, does not suffice to define the genus because it is only an indication of what **some general property the "region" has [the gene does, rather than what it is]**. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such **species [genes]** may achieve that result. The description requirement

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[6] At p. 4, continuation of paragraph 6.

[7] The Regents of the University of California v. Eli Lilly and Co., 43 USPQ2d 1398, at 1406.

of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.").

By substituting applicants' invention into the text of the Regents opinion, the Examiner seeks to impose the Federal Circuit's current view of the written description requirement for gene sequences upon applicants' claims, which are not genes, nor in fact biological sequences of any kind.[8] Although dicta in Regents and its predecessor cases suggest that chemical inventions may require greater description than,

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[8] The Federal Circuit's current view of the written description standard for gene sequences was developed through three cases. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), the Federal Circuit established the rule that conception of a gene sequence for the purpose of establishing priority of invention requires that the inventor have a clear idea of the detailed structure of the gene, *e.g.*, nucleotide sequence, sufficient to distinguish the gene from other materials, as well as a method for its preparation. In contrast, it is not sufficient to define the gene solely by its principal biological property, *e.g.*, encoding human erythropoietin, 18 USPQ2d 1016 at 1020-1022.

After Amgen, in Fiers v. Revel, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993), the Federal Circuit stated that the standard for conception of a DNA-based invention established in Amgen would also apply to the written description requirement for such inventions, 25 USPQ2d 1601 at 1606.

Finally, in Regents, the Federal Circuit confirmed its view of the written description for DNA inventions by holding that a claim directed to cDNA for human insulin was not adequately met by a specification disclosing the amino acid sequence of human insulin protein and a method of obtaining the cDNA sequence therefrom. Nor were claims directed to the genus of mammalian or vertebrate cDNAs encoding insulin sufficiently supported by disclosure of the sequence of a cDNA for rat insulin alone, 43 USPQ2d 1398 at 1404-1407.

for example, mechanical or software inventions,[9] the court has not decided a case that applies the *sui generis* standard for written description of gene sequences to chemical inventions, where there is greater predictability in the art. Thus, the Examiner cannot speak for the Federal Circuit by adopting the language it used in explaining its standards for written description of gene sequences to create a similar standard for a chemical invention, the type of invention claimed by applicants.

If anything at all can be distilled from the Federal Circuit's written description jurisprudence for gene sequences and applied to chemical inventions, it may be that one cannot merely describe such an invention by function alone.[10] And indeed, applicants have not so done. Pointedly, the molecules and related methods disclosed by applicants are not described solely in terms of biological function. Applicants have not disclosed "an antibody having an extended serum half-life," without more, analogous to the description of a "DNA encoding human erythropoietin" that was at issue in the Amgen case. Applicants provide extensive description of structures and physico-chemical properties of their inventions that comply with the current state of the law, and the PTO's own Written Description Examination Guidelines.[11, 12]

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[9] See for example, In re Hayes Microcomputer Products, Inc. Patent Litigation, 982 F.2d 1527, 25 USPQ2d 1241 (Fed. Cir. 1992).

[10] "We thus determined that, irrespective of the complexity or simplicity of the method of isolation employed, conception of DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility." Fiers v. Revel, 25 USPQ2d 1601 at 1604.

[11] The PTO Guidelines state:

"An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying

(continued...)

The specification discloses information regarding the structure of the molecules of the claimed invention, their physical and chemical properties, and correlations of their structure and function.

The description of the invention begins with a clear structural focus. One or more protein domains derived from IgG antibody, which possess the physico-chemical property of binding to the FcRb receptor, are linked to an antibody to be modified that already possesses a similar IgG-derived FcRb receptor binding domain (p. 24).[13] An example given is an IgG antibody linked to the CH2 and CH3 domains derived from an IgG Fc domain to create what is, in essence, an IgG antibody with a CH2-CH3 dimer in its Fc region (pp. 25, 38). This is diagramed in FIG. 1. Inclusion of the hinge domain of IgG is optional (pp. 39-42). Multimers of CH2-CH3 domains derived

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[11] (...continued)
characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Patent and Trademark Office Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, Written Description Requirement, §§ II(A)(3)(a) (emphasis added).

"For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession." Ibid. Footnote no. 42 (emphasis added).

[12] Which guidelines do not constitute substantive rule making, and hence do not have the force and effect of law. Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, Written Description Requirement.

[13] Page numbers refer to the specification of the instant application.

from IgG are also possible (p. 26). Specific methods for producing such molecules are also described (p. 25, 38-43). The CH2-CH3 domains can be essentially identical in sequence and structure to that of the antibody being modified, which sequence and structure is known in the art, or they can be derived from different IgG subclasses. For example, the FcRb binding domain from IgG1 Fc region can be linked to an IgG4 antibody (p. 26).

However, structures of the FcRb binding moieties of the instant invention are not limited to those found in native IgG molecules. As understood by the skilled artisan, FcRb receptor binding domains from IgG can serve as the starting point for generating mutated versions – *e.g.*, by making amino acid substitutions, additions or deletions – that are then tested for FcRb receptor binding (pp. 26, 56). Such mutated FcRb receptor binding domains may bind FcRb receptor more effectively than native IgG FcRb receptor binding domains (pp. 27, 15-19).

Rather than make modifications to the structure preexisting in the IgG Fc region responsible for binding FcRb receptor, libraries of peptides or polypeptides can be screened for specific binding to FcRb receptor to obtain FcRb binding moieties not derived from IgG (p. 26). Peptides and polypeptides can be tested for FcRb receptor binding according to the method disclosed in the specification for testing FcRb binding of modified IgG molecules, *i.e.*, by their ability to compete with unmodified IgG binding in a pH-dependent manner (pp. 28, 56). If such specific, pH-dependent binding is demonstrated, then it is expected that the peptides or polypeptide thus obtained will share critical structural attributes with the native FcRb binding moiety of IgG Fc regions. Peptide mimetics possessing structural elements related to those responsible for binding FcRb receptor found in native IgG Fc regions, selected modifications thereof, or

peptides selected for FcRb receptor binding can also be designed and utilized as FcRb binding moieties for purposes of the present invention (p. 19).

The specification also discusses physical and chemical properties of the modified antibodies, and of the modifying moieties, of the present invention. Most importantly, of course, all such modified antibodies bind FcRb receptors with enhanced avidity or affinity of binding, as compared to the unmodified antibodies, *e.g.* native IgG antibody (p. 27). Therefore, the avidity of binding of the modified antibody of the instant invention to FcRb may be less than or equal to 93 nM (p. 57), although the measured value depends on the method used to assay binding affinity of avidity. As a result of the increased affinity or avidity of binding FcRb receptor, as compared to antibodies that possess but a single FcRb binding moiety, modified antibodies of the instant invention exhibit at least 50% greater serum half-life as compared to the unmodified antibody, *e.g.*, native IgG antibody (p. 64).

Also important to the proper function of the invention is pH-dependent binding: modified antibodies of the instant invention bind FcRb receptor in the acidic environment of cellular endosomes (ca. pH 6.0), but are released when the FcRb receptor is again exposed to the slightly basic pH of the serum (ca. pH 7.4) (p. 28).

The Examiner, in further explaining the rejections under 35 U.S.C. § 112, ¶ 1 asserts that the disclosure is "insufficient to ... adequately describe the scope of the claimed invention ... and fails to provide sufficient relevant identifying characteristics that identify members of the genus."[14]

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[14] Office action p. 4, continuation of paragraph 6.

Applicants respectfully disagree and submit, as indicated by the review of the disclosure outlined above, that the written description is adequate to support the scope of the rejected claims, including those claims directed towards a genus. The specification contains sufficient description of the structure and physico-chemical properties of the various modified antibodies, and modifying moieties, of the instant invention to have reasonably conveyed to the skilled artisan possession by applicants of the generic invention at the time the application was filed.

Having satisfied the legal requirements of § 112, ¶ 1, as established by the Federal Circuit, applicants submit that the Examiner's rejections are in error and should be withdrawn. Applicants have not described their invention solely by reference to biological function. The invention is sufficiently described "so as to distinguish it from other materials."[15]

Applicants also submit that the rejections would be in error if asserted against the claims newly added by amendment herein. In particular, the new claims explicitly recite physico-chemical properties that further define the invention itself (*e.g.*, binding specificity, binding affinity and pH-dependent binding), and further clarify that, for present purposes, antibodies are the proteins to be modified by the methods of the present invention.

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[15] Amgen, Inc. v. Chugai Pharmaceutical Co., 18 USPQ2d 1016 at 1021.

The Examiner's Rejections Under 35 U.S.C. § 112, ¶ 2 Have Been Obviated by Amendment or Are in Error and Should be Withdrawn

The Examiner has rejected claims 12 - 43 under 35 U.S.C. § 112, ¶ 2, for failing particularly to point out and distinctly the subject matter of applicants' invention.

Specifically, the Examiner rejected claims 12, 17, 18, 25-27, 32, 33 and 40-43 as indefinite for reciting "region" because it is not clear what the term means. Applicants respectfully submit that "region" is not indefinite because its meaning would be clear to the skilled artisan, and the term therefore defines the subject matter of the invention with a reasonable degree of particularity and distinctness. The Examiner's rejection is therefore in error and should be withdrawn.

Solely in the interest of advancing prosecution, however, applicants have cancelled the rejected claims, thereby obviating the rejections.

The rejection would also be in error if asserted against the claims newly added by amendment herein. New claim 45 recites "immunoglobulin Fc region," new claim 46 recites "region consisting of an immunoglobulin hinge-CH2-CH3," and new claim 47 recites "region consisting of an immunoglobulin CH2-CH3." Applicants submit that use of the term "region" in the claims newly added by amendment herein fully complies with the requirements of § 112, ¶ 2: the skilled artisan will readily understand that all the aforementioned regions refer to well defined domains or parts of immunoglobulin molecules.

In addition, the Examiner rejected claims 12, 24, 25, 39, 40, 42 and 43 as indefinite for reciting "joining," or "joined" on the ground that it is not clear what the terms

mean.[16] Applicants respectfully submit that "joining" or "joined" are not indefinite because their meaning would be clear to the skilled artisan. The terms therefore define the subject matter of the invention with a reasonable degree of particularity and distinctness.

Applicants also note that the Examiner has relied on alleged prior art teaching "joining" in rejecting the instant claims under § 102 and § 103 (see below). Applicants presume that a claim cannot be rejected over art that allegedly teaches indefinite subject matter or that is described using indefinite terminology. Applicants respectfully submit that the Examiner's rejection is in error and should be withdrawn. Solely in the interest of advancing prosecution, however, applicants have cancelled the rejected claims, thereby obviating the rejections.

The Examiner's Rejections Under 35 U.S.C. § 102(a) Have Been Obviated by Amendment or Are in Error and Should be Withdrawn

The Examiner has rejected claims 12 - 19, 21, 22, 24 - 34, 36, 37, 39, 40, 42 and 43 as anticipated under 35 U.S.C. § 102(a) by Junghans, WO 97/43316 (Junghans). For the reasons advanced below, applicants respectfully submit that the rejections are in error and should be withdrawn, and would also be in error if asserted against the claims newly added by amendment herein.

Under § 102, a claim is properly rejected as anticipated only if the alleged anticipatory reference teaches each and every element of the claim. See M.P.E.P. §2131. The Examiner has not demonstrated that Junghans teaches every

[16] Applicants submit that this ground for rejection does not apply to the claims newly added by amendment herein, which do not recite "joining."

element of the rejected claims and has therefore failed to establish a prima facie case of anticipation. The rejections are therefore defective and should be withdrawn. Furthermore, applicants respectfully submit that the Examiner can make no such demonstration and that such rejections would be in error if asserted against the claims newly added by amendment herein.

With respect to claim 12, now cancelled, and the claims depending therefrom, Junghans does not teach a method of extending the serum half-life of a protein by joining a second region capable of binding to an FcRb receptor to a protein having a first region capable of binding to an FcRb receptor.[17]

With respect to claim 27, now cancelled, and the claims depending therefrom, Junghans does not teach a modified protein with an extended serum half-life comprising a first region capable of binding to an FcRb receptor and at least a second region capable of binding to an FcRb receptor.

With respect to claim 42, now cancelled, Junghans does not teach a method of increasing the binding avidity or affinity of a protein to a receptor comprising joining to a protein having a first region capable of binding to the receptor at least a second region capable of binding to the receptor.

With respect to claim 43, now cancelled, Junghans does not teach a modified protein with enhanced binding avidity or affinity for a receptor, comprising a first region capable of binding to the receptor and one or more additional linearly joined regions capable of binding to the receptor.

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[17] As used herein, the terms "FcRb," "FcRp" and "FcRn" are considered to be equivalent and refer to the same IgG Fc binding protein, binding to which effects a lower catabolic rate for IgG as compared to other immunoglobulin classes.

With respect to new claim 44, and the claims depending therefrom, all newly added by amendment herein, Junghans does not teach a method of extending the serum half-life of an antibody having a first moiety capable of binding to FcRb receptor, comprising linking to the antibody at least a second moiety capable of binding to FcRb receptor in a pH-dependent manner, wherein the antibody binds FcRb receptor with greater avidity at pH 7.4 after adding the additional moiety or moieties.

With respect to new claim 49, and the claims depending therefrom, all newly added by amendment herein, Junghans does not teach an antibody with an extended serum half-life comprising a first moiety capable of binding FcRb receptor and at least a second moiety capable of binding FcRb receptor in a pH dependent manner, wherein the second moiety comprises an immunoglobulin CH3 region that contributes to FcRb receptor binding, which second moiety confers upon the antibody greater avidity of binding FcRb receptor at pH 7.4 than the avidity of binding of the antibody lacking the second moiety.

As presently claimed, applicants' invention comprises methods whereby an antibody, already capable of binding FcRp receptor, is modified to effect an increase in its serum half-life by linking to it at least a second moiety capable of binding to an FcRb receptor. Thus, an element of the claimed methods is an antibody already capable of binding FcRp. This element is taught nowhere in Junghans.

The Examiner states that "Junghans teaches a method for producing an antibody which has an extended half-life ... comprising modifying the structure of an antibody ... which has a first FcRn binding domain."[18] Applicants respectfully submit that the Examiner has misconstrued the teachings of

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[18] Office action p. 5, paragraph 10.

Junghans and that Junghans does not anticipate the claimed invention.

Junghans does not teach producing an antibody which has an extended half-life by modifying the structure of an antibody which has a first FcRn binding domain. Rather, Junghans teaches:

> [P]hysiologically active molecules which have extended half-lives in the circulatory system of a subject [that are] extended by modifying their structure such that they are capable of binding to the IgG protection receptor FcRp. By modifying the physiologically active molecules in this manner, the invention takes advantage of the discovery that ... modifying physiologically active molecules such that they are capable of binding the IgG protection receptor FcRp allows these molecules to escape lysosomal catabolism and remain in the circulation of a subject for longer periods of time.[19]

Thus, it is clear that Junghans did not contemplate modifying the structure of an antibody, *e.g.*, certain IgG subclasses, that already are capable of binding FcRp, to further extend serum half-life. If it were otherwise, the language "modifying their structure such that they are capable of binding ... FcRp" (emphasis added) would be nonsensical, because this statement necessarily implies that the molecules were not capable of binding FcRp before being modified.

This reading is further validated by the exemplary physiologically active molecules recited by Junghans, **not one of which binds FcRp if unmodified**:

> proteins and peptides, *e.g.*, immunoglobulins, immunoglobulin fragments or portions, *e.g.*, all or a portion of IgG3, IgA, IgD, IgE, IgM, and other nonimmunoglobulin molecules including cytokines, *e.g.*, TGF-β, interleukin-2, interleukin-10, interleukin-12, GM-CSF, and vaccine immunogens, *e.g.*, gp120 for HIV, HBSAg of hepatitis B, hemaglutinin of influenza virus, coat protein of

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[19] Specification of WO 97/43316, p.2, lines 21-30.

> respiratory syncytial virus, tetanus toxoid of C. tetani, outer membrane proteins of P. pneumoniae, V. cholerae, S. typhae, L. monocytogenes, and M. tuberculosis.[20]

Also relevant are the molecules recited in the examples, to which are attached a carrier molecule that binds to FcRp, including IgM (example IV), IgA (example V), HBSAg (example VI), gp120 (example VII), glycophorin A (example VIII), IL-10 and TGFβ (example IX), and IL-2 (example X). None of the afore-mentioned molecules bind FcRp so as to be protected from catabolism, unless modified by association with a carrier molecule.

That Junghans recites immunoglobulins as examples of physiologically active molecules does not change the conclusion that Junghans only disclosed modifying molecules that lack FcRp binding function so as to confer this capability upon the molecules so modified. This is made clear by recitation, as examples of immunoglobulins, of IgA, IgD, IgE, and IgM, the immunoglobulin classes known not to bind FcRp, and therefore to have short serum half-lives.[21] Furthermore, the only IgG subclass recited by Junghans as an example of an immunoglobulin that can be modified to extend its serum half-life is IgG3. Three of the four human IgG subclasses (i.e., IgG1, IgG2 and IgG4) bind FcRp, and therefore have long serum half-lives.[22] Antibodies of the IgG3

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[20] Specification of WO 97/43316, p.2, lines 34-36 to p.3, lines 1-5.

[21] See Appendix C: Table 4-2, Properties and biological activities of classes and subclasses of human serum immunoglobulins, Goldsby, R.A., et al., Immunology, 4th Ed. (2000), W.H. Freeman and Co., New York.

[22] See Appendix C.

subclass, in contrast, except for rare allotypes do not bind FcRp.[23]

It is reasonable to conclude that if Junghans had contemplated modifying immunoglobulins already capable of binding FcRp, Junghans would have included as an example one of the three IgG subclasses possessing this function. This is made even more likely because, in addition to being the only IgG subclass lacking FcRp binding, IgG3 is one of the least prevalent subclasses found in normal human serum (1 mg/ml for IgG3 vs. 9 mg/ml for IgG1). One would have expected the most prevalent subclass, IgG1, to be recited instead.

Throughout the specification, Junghans also teaches that modifications made to physiologically active molecules to confer upon them the ability to bind FcRp must not confer binding to an Fc receptor that mediates immune effects, or alternatively, must not confer binding to complement.[24] Thus, all molecules taught by Junghans that are modified to bind FcRp either do not bind Fc receptor, or do not bind complement.

The methods of modification and modified antibodies of the instant invention are quite different: applicants teach methods of modification wherein the antibodies so created are

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[23] Most allotypes of IgG3 possess an arginine residue at amino acid position 435, whereas rare allotypes possess a histidine, the same residue appearing at position 435 of IgG1. Mutational analysis indicates that when position 435 of IgG1 is changed from histidine to a different amino acid, including arginine, IgG1 binding to FcRp is lost, and serum half-life is diminished. See, *e.g.*, Appendix D: West, A.P., et al., Crystal structure and immunoglobulin G binding properties of the human major histocompatibility complex-related Fc receptor, Biochemistry, 39:9698-9708 (2000).

[24] Junghans specification at p. 3, lines 8-14; p. 3, lines 32-36 and p. 4, line 1; p. 5, lines 7-12; p. 6, lines 3-6; p. 6, lines 23-29; p. 7, lines 1-9; p. 9, lines 24-30; p. 16, lines 29-35; p. 17, lines 17-22; p. 19, lines 22-36 and p. 20, lines 1-3; p. 29, lines 3-6; and p. 32, lines 15-18.

able to bind Fc receptors, or alternatively, are able to bind complement. For example, as taught by applicants, if one joins a Fc region of IgG to an antibody already capable of binding FcRp so as to extend its serum half-life, the Fc region so joined confers upon the whole antibody the ability to bind to Fc receptor and/or complement, because the Fc region of IgG (the added moiety) comprises amino acid sequences capable of binding Fc receptors and complement. Thus, Junghans' teaching of modified molecules that do not bind Fc receptors or complement does not anticipate the modified antibodies of the instant invention that do bind Fc receptors, or alternatively, that bind complement.

To further explain the rejections under § 102(a), the Examiner states that Junghans teaches "a modified antibody which has an extended half-life in a subject comprising at least a first and second FcRn binding domain physically linked to a constant region of the antibody."[25] In support of this statement, the Examiner points to claims 1, 5, 6, 10 and Table 1 of Junghans.

Applicants respectfully disagree that Junghans teaches such a modified antibody.

Junghans claim 1 pertains to a physiologically active molecule having an extended serum half-life, the structure of which is modified to include an amino acid sequence that binds to FcRp, but not to Fc receptor. Thus, claim 1 does not teach a modified antibody comprising at least a first and second FcRp binding domain physically linked to a constant region of the antibody.

Junghans claim 5 depends multiply from Junghans claims 1 through 4 and further limits the claim to physiologically active molecules that are immunoglobulins, or a portion thereof. As discussed in detail above, the immunoglobulins

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[25] Office action, p. 5, paragraph 10.

disclosed by Junghans are those classes and subclasses that are not capable of binding FcRp prior to modification.

Junghans claim 6 depends from claim 5 and further limits the claim to physiologically active molecules that are immunoglobulins limited to the classes and subclasses IgG3, IgA, IgD, IgE, and IgM, or portions thereof. None of these classes and subclasses of immunoglobulins are capable of binding FcRp without modification.

Junghans claim 10 pertains to a physiologically active molecule having an extended serum half-life, the structure of which is modified to include at least a portion of an antibody that specifically binds FcRp. Like claim 1, claim 10 does not teach a modified antibody comprising at least a first and second FcRp binding domain physically linked to a constant region of the antibody.

In further explanation of the rejections under § 102(a), the Examiner states that Junghans teaches "an IgA molecule which is altered recombinantly to possess three FcRn binding domains 'KTLMISRTP,''VLHG,' and 'HNHY'."[26]

Applicants respectfully disagree that Junghans teaches an IgA molecule that is altered to possess three FcRn binding domains. The skilled artisan will understand that what is meant by the term "FcRn binding domain" refers to a domain sufficient for binding FcRn, as opposed to a subregion of such a domain that, although necessary for binding, is itself insufficient to effect such binding. The amino acid sequences recited by the Examiner fall into the latter category, i.e., sequences apparently necessary, but not sufficient, to support binding of FcRn. Indeed, Junghans does not refer to the recited sequences as "FcRn binding domains." Rather, Junghans states that "regions of the IgG molecule which are involved in binding to the FcRn receptor ... ***include*** KTLMISRTP ... VLHQ

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[26] Office action, p. 5, paragraph 10.

... and HNHY"[27] (emphasis added). Thus, the amino acids recited by the Examiner are regions that contribute to formation of a FcRn binding domain, but are not sufficient for this function, and hence are not properly termed FcRn binding domains. Thus, Junghans, not having taught an IgA molecule altered to possess three FcRn binding domains, does not anticipate the instant invention.

The Examiner further states that Junghans teaches "an antibody or antigen-binding fragment of an antibody produced against the FcRp which is included as a modification to another molecule," which other molecule can be an immunoglobulin, and that the molecule of the instant invention appears to be the same as that taught by Junghans.[28, 29]

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[27] WO 97/43316, p. 7, lines 30 - 36 and p. 8, line 1.

[28] Office action, p. 5-6, paragraph 10.

[29] The Examiner, referring to the C.C.P.A. case In re Best, 195 U.S.P.Q. 430, also states that "since the Patent Office does not have the facilities for examining and comparing the molecule of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the molecule of the instant invention and that of the prior art." Office action, p. 6, continuation of paragraph 10.

The Examiner's citation to In re Best does not relieve the Examiner of establishing a prima facie case of anticipation, which the Examiner has failed to do.

In re Best discusses the burden of proof assignable to the applicant after the PTO has made out a prima facie case of inherent anticipation. The court stated that after the PTO makes a prima facie case that a functional limitation important for patentability is an inherent characteristic of the prior art, the burden shifts to the applicant to prove that the prior art does not in fact possess that characteristic. However, "in relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112. In other words, the Examiner must first make out a prima facie case of inherent anticipation.

(continued...)

Junghans indeed teaches physiologically active molecules modified to include at least a portion of an antibody that is raised against the IgG protection receptor FcRp and which specifically binds to the IgG protection receptor FcRp.[30] In other words, Junghans teaches modifying physiologically active molecules by joining to them the antigen binding portion of an antibody, *e.g.*, $F(ab')_2$, raised against the FcRp receptor. However, this is not what applicants have invented and claimed.

With respect to claims 12 and 42, now cancelled, and claim 44, newly added by amendment herein, Junghans does not teach the element, present in all the aforesaid claims, that the protein or antibody to be modified by the claimed methods have a first region or moiety capable of binding to an FcRb receptor. As discussed above, the physiologically active molecules contemplated and taught by Junghans lack the first region or moiety capable of binding to an FcRb receptor.

With respect to claims 27 and 43, now cancelled, Junghans does not teach that the modified protein have had a first region or moiety capable of binding to an FcRb receptor prior to modification.

With respect to claim 49, newly added by amendment herein, Junghans does not teach an antibody comprising a second moiety capable of binding FcRb receptor that contains

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[29] (...continued)
In the present case, the Examiner has failed to make out a prima facie case of inherent anticipation, and the applicant is therefore under no burden to distinguish the instant invention from the teachings of Junghans, regardless whether or not the PTO has "the facilities for examining and comparing the molecule of the instant invention to those of the prior art."

[30] WO 97/43316, p. 9, lines 35-36 to p. 11, lines 1-16.

an immunoglobulin CH3 region that contributes to FcRb receptor binding.[31]

In further explanation of the rejections under § 102(a), the Examiner states that Junghans teaches "IgG molecules that can be joined, including as a fusion protein, to carrier molecules comprising FcRp binding 'carriers,'" as well as compositions containing such proteins.[32]

Although Junghans states that physiologically active molecules can be modified by coupling of two nucleic acid molecules, one of which encodes the physiologically active molecule and another of which encodes an amino acid sequence capable of binding to the FcRp receptor to generate a fusion

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[31] Even if an entire antibody molecule raised against FcRb receptor were used to modify a physiologically active molecule, the modified molecules so created would not anticipate the instant invention.

If the anti-FcRb antibody used for modification were of the IgG3, IgA, IgD, IgE, or IgM isotype, then as is well known in the art the Fc regions are not capable of binding to an FcRb receptor (see, *e.g.*, Appendix C), and logically, the Fc regions do not contribute to FcRb receptor binding. As a result, such antibodies necessarily lack an immunoglobulin CH3 region that contributes to FcRb receptor binding, an element present in new claim 49 and the claims depending therefrom.

Alternatively, if the anti-FcRb antibody used to modify a physiologically modified antibody were IgG1, IgG2 or IgG4, Junghans teaches that its fully functional Fc region must be excluded. Thus, the antibodies of the instant invention, possessing fully functional Fc regions capable of binding Fc receptors that mediate immune effects and/or complement, are not anticipated. This is true because all IgG subclasses bind Fc receptors that mediate immune effects (see *e.g.*, Appendix C) but, as discussed above, Junghans teaches that physiologically active molecules modified according to his methods must not bind such Fc receptors. Therefore, to create modified physiologically active molecules using IgG according to Junghans, one must exclude a functional Fc region to prevent its binding to Fc receptors mediating immune effects.

[32] Office action, p. 6, continuation of paragraph 10.

protein,[33] Junghans does not teach linking of IgG molecules to FcRp binding carrier molecules per se.

As discussed above, Junghans indicates that physiologically active molecules to be modified according to his teachings are those not capable of binding FcRp prior to modification. Thus, while Junghans states that physiologically active molecules can be immunoglobulins,[34] it is clear these are limited to those classes and subclasses not capable of binding FcRp without modification (*i.e.*, IgG3, IgA, IgD, IgE and IgM). As a result, Junghans cannot have taught linking IgG as a class of immunoglobulins to an amino acid sequence capable of binding FcRp receptor because the class IgG comprises subclasses IgG1, IgG2 and IgG4 that are all able to bind FcRp without modification: an element expressly excluded by Junghans' teachings. Thus, Junghans cannot anticipate the instant invention directed to modifying a protein having a first region capable of binding to FcRb receptor. At most, Junghans may have taught joining IgG3,[35] but not the class of IgG generally, to an amino acid sequence capable of binding FcRp.

In further explanation of the rejections under § 102(a), the Examiner states that the sequences taught by Junghans and the region capable of binding to an FcRb receptor of the formerly pending, now cancelled, claims appear to be the same, absent a showing of any differences.[36, 37] Simply

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[33] WO 97/43316 at p. 11, lines 28-33.

[34] WO 97/43316 at p. 5, lines 19-21.

[35] That is, the great majority of IgG3 allotypes that do not bind FcRp without modification.

[36] Office action, p. 6, continuation of paragraph 10.

[37] The Examiner again cites to the C.C.P.A. case In re Best, stating that "since the Patent Office does not have the

(continued...)

put, identity between a region as recited in the formerly pending claims and sequences taught by Junghans is irrelevant because applicants had not claimed a region capable of binding a FcRb receptor per se. Rather, applicants claimed methods of extending the serum half-life of a protein having a first FcRb binding region by linking to the protein at least a second FcRb binding region, and additionally claimed proteins so modified. Whereas Junghans teaches regions capable of binding FcRb, as discussed above, Junghans does not teach other elements of the formerly claimed methods and compositions. Thus, Junghans cannot anticipate the invention as had been claimed. The Examiner's rejections are therefore in error and should be withdrawn.

The Examiner's rejections would also be in error if asserted against the claims newly added by amendment herein for similar reasons. Specifically, applicants do not claim a moiety capable of binding a FcRb receptor per se. Rather, applicants claim methods of extending the serum half-life of an antibody having a first FcRb binding moiety by linking to the antibody at least a second FcRb binding moiety, and additionally claim antibodies so modified. Whereas Junghans teaches regions capable of binding FcRb, as discussed above, Junghans does not teach other elements of the instant invention as presently claimed.

In further explanation of the rejections under § 102(a), the Examiner states that the term "joining" encompasses Junghans' teaching of insertion of the Brambell motif into a protein as well as the modification of nucleic

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[37] (...continued)
facilities for examining and comparing the molecule of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the molecule of the instant invention and that of the prior art." As discussed in footnote 29, the Examiner is not relieved of the burden of establishing a prima facie case of anticipation.

acid sequences to encode a Brambell motif amino acid sequence.[38, 39]

During examination, the claims must be interpreted as broadly as their terms reasonably allow. This means that the words of the claim must be given their plain meaning. In other words, they must be read as they would be interpreted by those of ordinary skill in the art.[40] See also M.P.E.P. § 2111.01.

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[38] Office action, p. 6, continuation of paragraph 10.

[39] Applicants submit that this ground for rejection does not apply to the claims newly added by amendment herein, which do not recite "joining."

[40] "Although the PTO must give claims their broadest reasonable interpretation, this interpretation must be consistent with the one that those skilled in the art would reach. See In re Morris, 127 F.3d 1048, 1054, 44 U.S.P.Q.2D (BNA) 1023, 1027 (Fed. Cir. 1997) ('The PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art . . . .'); In re Bond, 910 F.2d 831, 833, 15 U.S.P.Q.2D (BNA) 1566, 1567 (Fed. Cir. 1990) ('It is axiomatic that, in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation consistent with the specification, . . . and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art.') (emphasis added); see also M.P.E.P. § 2111.01 ('The words of a claim . . . must be read as they would be interpreted by those of ordinary skill in the art.'). Prior art references may be 'indicative of what all those skilled in the art generally believe a certain term means . . . [and] can often help to demonstrate how a disputed term is used by those skilled in the art.' Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1584, 39 U.S.P.Q.2D (BNA) 1573, 1578-79 (Fed. Cir. 1996). Accordingly, **the PTO's interpretation of claim terms should not be so broad that it conflicts with the meaning given to identical terms in other patents from analogous art**. Cf. Morris, 127 F.3d at 1056, 44 U.S.P.Q.2D (BNA) at 1029 (approving the board's definition of claim terms consistent with their definitions in CCPA cases)." In re Cortright, 165 F.3d 1353; 49 U.S.P.Q.2D 1464 (Fed. Cir. 1999) (emphasis added).

Applicants respectfully submit that the Examiner's afore-mentioned interpretation of the term "joining" is not reasonable because it is inconsistent with the plain meaning of the term. No skilled artisan would interpret "joining," as used by applicants, to include amino acid insertion or substitution, as asserted by the Examiner. As used by applicants, the term "joining" does not have a specialized meaning distinct from that of standard English.[41] Thus, applicants respectfully submit that any rejection based upon the Examiner's overly broad interpretation of "joining" is in error and should be withdrawn.[42]

Even if "joining" could reasonably be construed as encompassing the type of modifications taught by Junghans, the invention as formerly claimed is still not anticipated by Junghans. As explained above, Junghans teaches that modification, by whatever the means, must not result in a molecule that is capable of binding an Fc receptor that mediates immune effects and/or complement. In contrast, molecules modified by the methods of the invention as formerly claimed[43] are capable of binding Fc receptor and/or complement. Therefore, the modified molecules of Junghans and those modified by the methods of the invention as formerly claimed are <u>different</u>, and Junghans is not anticipatory.

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[41] Reference to a dictionary yields the following common definitions of "join," the verb stem of the present participle "joining": 1. To bring or put together or in contact; connect. 2. To come into contact or union with. 3. To bring together in a particular relation or for a specific purpose, action , etc.; unite. Random House College Dictionary, Revised Ed. (1984), Random House, Inc., New York. None of primary or subsidiary meanings of "joining" support the Examiner's construction of the term.

[42] Applicants submit that this ground for rejection does not apply to the claims newly added by amendment herein, which do not recite "joining."

[43] And of the antibodies as presently claimed.

The Examiner's Rejections Under 35 U.S.C. § 103 Have Been Obviated by Amendment or Are in Error and Should be Withdrawn[44]

The Examiner has rejected claims 12 - 43 under 35 U.S.C. § 103(a) as having been obvious over WO 97/43316 to Junghans (Junghans), in view of U.S. Patent No. 5,702,946 to Doerschuk, U.S. Patent No. 5,766,897 to Braxton, and Immunologic Research (1997), 16(1):29-57 to Junghans (Junghans II). For the reasons advanced below, applicants respectfully submit that the rejections are defective and should be withdrawn, and would also be in error if asserted against the claims newly added by amendment herein.

There are three requirements to establish a prima facie case of obviousness. First, there must be some suggestion or motivation contained in the cited references, or in the knowledge generally available to the skilled artisan, to combine reference teachings to reach the claimed invention. Second, the prior art must provide a reasonable expectation that the suggested combination will be successful. Third, the prior art reference must teach or suggest all the claim limitations. See M.P.E.P. § 2143. The Examiner has the initial burden of factually supporting any prima facie conclusion of obviousness. See M.P.E.P. § 2142.

The Examiner has failed to make the necessary factual showing. The Examiner's rejections grounded in obviousness are therefore defective and should be withdrawn.

The Examiner states that "it would have been prima facie obvious ... to have used a human antibody with the anti-IL-8 specificity of Doerschuk as the modified antibody in the invention of Junghans given the teachings of Junghans [II] of

[44] Applicants acknowledge the Examiner's reference to 35 U.S.C. §§ 102(f), 102(g), 103(a) and 103(c), and 37 C.F.R. §1.56. Applicants submit that they are fully in compliance with respect thereto.

the saturation of FcRn at high serum IgG concentrations and the disclosure of Braxton of the need for increasing the short half-life of therapeutic proteins after administration for use as a therapeutic agent in humans as disclosed by Doerschuk."[45, 46, 47]

Although the Examiner proffers a generalized motivation to increase the short half-life of therapeutic proteins, the Examiner has failed to show a specific motivation to combine the cited references, or that there exists in the prior art a reasonable expectation of success of so doing. The Examiner has also failed to show that the cited references teach or suggest all the claim limitations. For these reasons, The Examiner's rejections based on obviousness are defective and should be withdrawn.

The references cited by the Examiner, in fact teach away from the instant invention. A skilled artisan, considering the teachings of Junghans and Braxton, would not have been motivated to modify a human antibody with the anti-

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[45] Office action, paragraph 12, as continued on p. 8.

[46] The Examiner, in the subsequent sentence, repeats the reason for the obviousness rejection, which reason appears to be slightly different in form, but identical in content to the reason of the prior sentence. Thus, applicants treat the reason given in the second sentence as the same as the one presented in the first sentence.

[47] Applicants agree that Junghans II teaches that "at low serum IgG concentrations the FcRn receptor binds all endocytosed IgG and efficiently returns the IgG to circulation, yielding a long [net] IgG survival, but at high IgG concentrations, the receptor is saturated by IgG and the major fraction of the IgG is unbound by the receptor and passes to catabolism, yielding a more rapid net catabolism and abbreviated survival," with the proviso that not all IgG subclasses bind FcRn, and hence are protected from catabolism. However, applicants fail to perceive the relevance of this teaching to the matter of the alleged obviousness of the rejected claims. Therefore, applicants respectfully invite the Examiner to further explain the relevance of Junghans II, before applicants comment further on its teachings.

human IL8 specificity of Doerschuk to comprise a first and a second FcRn binding domain.

As discussed at length above, Junghans teaches modification only of physiologically active molecules, including immunoglobulins, that initially are not capable of binding FcRn, so as to confer FcRn-binding capability. That is, Junghans instructs the skilled artisan not to modify physiologically active molecules that already possess a FcRn binding region.

However, the anti-human IL8 monoclonal antibodies taught by Doerschuk are mouse antibodies of the IgG1 and IgG2a subclasses, or isotypes,[48] and as is well known in the art, both these murine subclasses have extended serum half-lives reflecting proven or likely binding to FcRn, and thereby protection from catabolism.[49] Because Doerschuk teaches monoclonal antibodies already capable of binding FcRn, the skilled artisan, following the teachings of Junghans, would be lead away, rather than toward, the instant invention.

Doerschuk also teaches production of Fab fragments of chimeric mouse monoclonal antibodies specific for human IL8.[50] As is well known in the art, Fab fragments, absent modification, do not bind FcRn. Following the teachings of Junghans, a skilled artisan might be motivated to modify a Fab

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[48] See Table I, column 17 of Doerschuk, U.S. Patent No. 5,702,946.

[49] Murine IgG1 binds murine FcRn and has an extended serum half life; see Appendix E, Medesan, C., et al., "Delineation of the amino acid residues involved in transcytosis and catabolism of mouse IgG1," J. Immunol. (1997), 158:2211-2217. IgG2a, like IgG1 has an extended serum half-life; see Appendix F, U.S. Patent No. 6,277,375, column 20, lines 14-16. Both IgG1 and IgG2a possess a His residue at amino acid position 435, mutation of which abolishes FcRn binding and rescue from catabolism; see Appendix E and Appendix F, Table I and column 19, lines 41-42.

[50] U.S. Patent No. 5,702,946, columns 19-21, 23-25.

to a include an amino acid sequence that binds FcRn, treating Fab like IgA or IgM, other immunoglobulin molecules lacking FcRn binding regions of which Junghans teaches modification. However, these combined teachings fail to teach one or more elements of the invention defined by the rejected, now cancelled claims, or by the invention as presently claimed.

In considering the teachings of Braxton, the skilled artisan would also be lead away, not toward, the invention defined by the rejected, now cancelled claims, or by the invention as presently claimed. Braxton teaches that development of protein therapies is hampered by the short half-life of proteins administered to patients because such proteins are quickly cleared from the circulation by the kidneys.[51] To address this problem, Braxton teaches that polyethylene glycol (PEG) moieties can be attached to cysteine residues of the protein to increase its serum persistence. Braxton also teaches that two or more proteins can be linked together by one or more PEG moieties to create dimers or multimers of proteins.

Thus, in considering the teachings of Braxton, the skilled artisan seeking to solve the problem of short protein serum half-life would be motivated to PEGylate the protein.

In contrast, the invention defined by the rejected, now cancelled claims, and by the invention as presently claimed, pertains to increasing serum half-life of proteins, including antibodies, by a specific mechanism, *i.e.*, increasing the probability that a protein will bind the FcRn receptor by linking to the protein one or more additional FcRn binding regions. Further, the invention as formerly and presently claimed pertains to a mechanism of protein catabolism mediated not by the kidneys per se, but rather by vascular endothelial cells generally. Thus, Braxton, teaching

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[51] U.S. Patent No. 5,766,897, column 1, lines 46-51.

a fundamentally different approach to increasing serum persistence of proteins, teaches away from the invention as formerly and presently claimed, rather than toward it.

In further explaining the rejections under § 103, the Examiner states that applicants have not provided evidence that individual sequences or combinations of sequences taught by Junghans are not sufficient to bind FcRn. As applicants understand, this statement reflects the Examiner's belief that a number of discrete amino acid sequences discussed by Junghans are separately FcRn binding regions, each alone sufficient for this purpose, as opposed merely to constituents of such domains. The position of applicants that such discrete sequences are necessary but insufficient was discussed in their response to the prior Office Action mailed February 16, 2000, and restated above, in the section of this response devoted to the Examiner's rejections under 35 U.S.C. § 102(a), which discussions are incorporated here by reference in their entireties.

Although applicants contend it is clear from Junghans alone that such sequences are not sufficient for FcRn binding, in the prior response applicants drew the Examiner's attention to Zuckier et al.,[52] which demonstrates that the discrete domains discussed by Junghans contribute to FcRn binding, but are not FcRn binding domains unto themselves. Through an oversight, applicants failed to include a copy of the Zuckier reference with the prior response, and do so now, enclosed in Appendix G.

The Examiner also states that, by virtue of Junghans' teaching of insertion of the Brambell motif into a protein, Junghans thereby teaches "joining," an element of the

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[52] Zuckier et al., "Chimeric human-mouse IgG antibodies with shuffled constant region exons demonstrate that multiple domains contribute to in vivo half-life," Cancer Research (1998), 58(17):3905-3508.

methods of the instant invention.[53] Applicants contend that the Examiner has read more into the term "joining" than is reasonable, as discussed above, which discussion is incorporated here by reference.

The Examiner also notes that the instant claims are not limited to IgG1, IgG2a or IgG2b, implying that the claims should be so limited. In their prior response, applicants' recitation of the aforementioned subclasses of IgG were exemplary and not limiting. Thus, there is no reason the formerly pending claims, now cancelled, or the claims newly added by amendment herein, should be so limited.

As discussed above, Junghans teaches that the serum half-life of physiologically active molecules lacking an FcRp binding region can be increased by modifying such molecules to include an amino acid sequence that binds FcRp. Examples given by Junghans include the human immunoglobulins IgG3, IgA, IgD, IgE and IgM, as well as a number of other non-immunoglobulin proteins.[54] By implication, Junghans teaches away from the human and mouse IgG subclasses known to possess a first FcRp binding domain in their Fc region, and away from any other proteins lacking a first region capable of binding to an FcRb receptor.[55] Thus, the previously pending claims, now cancelled, were directed to any protein, not just IgG subclasses, having a first region capable of binding FcRb receptor, and the claims newly added by amendment herein are

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[53] Applicants submit that this ground for rejection does not apply to the claims newly added by amendment herein, which do not recite "joining."

[54] Office action p. 5, lines 19 - 25 and Examples IV - X.

[55] Human IgG subclasses that bind FcRp include IgG1, IgG2 and IgG4. See Appendix C. Mouse IgG subclasses that bind FcRp include IgG1, IgG2a, and IgG3. In the prior response, applicants incorrectly identified IgG2b as an example of an IgG subclass that binds FcRp, when in fact it does not. See Appendix E, p. 2215. Applicants regret this error.

directed to any antibody, not just IgG subclasses, having a first region capable of binding FcRb receptor.

CONCLUSION

Applicants respectfully submit that the amendments and remarks herein place the present claims in condition for allowance, and earnestly solicit the same. Applicants invite the Examiner to call the undersigned attorney of record if the Examiner believes that any remaining matters might be resolved more expeditiously by means of a telephonic interview.

Respectfully submitted,

4 JAN 2002

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